CHRONIC TOXICITY SUMMARY

ARSENIC AND ARSENIC COMPOUNDS

Molecular Formula	*Synonyms*	*Molecular Weight*	*% As by Weight*	*CAS Reg. No.*
As	Arsenic black, metallic arsenic	74.92 g/mol	100%	7440-38-2
As_2O_3	Arsenious acid, crude arsenic, white arsenic	197.82 g/mol	75.7%	1327-53-3
As_2O_5	Arsenic anhydride, arsenic oxide, arsenic oxide anhydride	229.82 g/mol	41.3%	1303-28-2
$AsHNa_2O_4$	Arsenic acid disodium salt, disodium arsenate, sodium arsenate dibasic	185.91 g/mol	40.3%	7778-43-0

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.03 mg As/m^3**
Oral reference exposure level	**0.0003 mg/kg bw-day** (based on U.S. EPA RfD)
Critical effect(s)	Decreased fetal weight; increased incidences of intrauterine growth retardation and skeletal malformations in mice
Hazard index target(s)	Development (teratogenicity); cardiovascular system; nervous system

II. Physical and Chemical Properties (For metallic arsenic except as noted)

(from HSDB, 1995, and CRC, 1994 except as noted)

Description	As: Yellow, black or gray solid As_2O_3: White solid
Molecular formula	See above
Molecular weight	See above
Density	As: 5.727 g/cm^3 @ 14°C As_2O_3: 3.74 g/cm^3
Boiling point	As: 613°C (sublimes) (ACGIH, 1992); As_2O_3: 465°C
Melting point	As: 817°C @ 28 atm As_2O_3: 312.3°C
Vapor pressure	1 torr @ 372° C
Solubility	As: soluble in nitric acid; insoluble in water Oxides: soluble in water Salts: soluble in water
Conversion factor	Not applicable

III. Major Uses or Sources

Ore refining processes, including the smelting of copper and lead, are the major sources by which arsenic dust and inorganic arsenic compounds are released (Grayson, 1978). Arsenic trioxide (As_2O_3) is the most commonly produced form of arsenic. As_2O_3 is used as a raw material for the production of other inorganic arsenic compounds, alloys, and organic arsenic compounds. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 11,303 pounds of arsenic (CARB, 2000).

IV. Effects of Human Exposure

Smelter workers, exposed to concentrations of arsenic up to 7 mg As/m^3, showed an increased incidence in nasal septal perforation, rhinopharyngolaryngitis, tracheobronchitis, and pulmonary insufficiency (Lundgren, 1954; as cited in U.S. EPA, 1984).

In a case-control study, copper smelter workers (n = 47) exposed to arsenic for 8-40 years (plus 50 unexposed controls matched for age, medical history, and occupation) were examined by electromyography and for nerve conduction velocity in the arms and legs (Blom *et al.*, 1985). The workers were found to have a statistically significant correlation between cumulative exposure to arsenic and reduced nerve conduction velocities in three peripheral nerves (upper and lower extremities). Slightly reduced nerve conduction velocity in 2 or more peripheral nerves was reported as "more common" among arsenic exposed workers. Minor neurological and electromyographic abnormalities were also found among exposed workers. Occupational exposure levels were estimated to be 0.05-0.5 mg As/m^3, with As_2O_3 the predominant chemical form. Except for three arsenic exposed workers who had long-term exposure to lead, exposure to other heavy metals was insignificant.

The smelter workers, described by Blom *et al.* (1985) (number of controls reduced to 48), were further examined for prevalence of Raynaud's phenomenon and for vasospastic tendency by measurement of finger systolic pressure at 10°C and/or 15°C relative to that at 30°C (FSP%) (Lagerkvist *et al.*, 1986). The FSP% was found to covary with the duration of exposure to arsenic, and the prevalence of Raynaud's phenomenon was significantly increased among exposed workers. Daily arsenic uptake was estimated at less than 300 μg/day and was confirmed with urinary excretion data.

Hyperpigmentation and hyperkeratinization were observed in workers exposed to 0.4–1 mg/m^3 inorganic arsenic for two or more years (Perry *et al.*, 1948).

Mazumder *et al*. (1998) investigated arsenic-associated skin lesions of keratosis and hyperpigmentation in 7683 exposed subjects in West Bengal, India. While water arsenic concentrations ranged up to 3400 μg/L, over 80% of the subjects were consuming water with < 500 μg/L. The age-adjusted prevalence of keratosis was strongly related to water As concentration, rising from zero in the lowest exposure level (< 50 μg/L) to 8.3% for females

drinking water containing >800 µg As/L, and 0.2 to 10.7% in males, respectively. A similar dose-response was observed for hyperpigmentation: 0.3 to 11.5% for females, and 0.4 to 22.7% for males. Overall, males had 2-3 times the prevalence of both keratosis and hyperpigmentation than females apparently ingesting the same doses of arsenic per body weight. Subjects that were more than 20% below standard body weight for their age and sex had a 1.6-fold increase in the prevalence of keratoses, suggesting that malnutrition may play a role in increasing susceptibility.

Dermatitis and irritation of the mucous membranes have been observed in arsenic exposed workers (Vallee *et al.*, 1960).

Chronic exposure to arsenic has been associated with decreased birth weight and an increased rate of spontaneous abortion in female smelter workers. However, this association is confounded by the presence of other toxicants in the smelting process, including lead (Nordstrom *et al.*, 1979).

Hepatic fatty infiltration, central necrosis, and cirrhosis were observed in two patients who ingested As_2O_3 (1% in Fowler's solution) for three or more years (Morris *et al.*, 1974). Daily consumption of 0.13 mg As/kg in contaminated well water resulted in the chronic poisoning and death of four children; at autopsy, myocardial infarction and arterial thickening were noted (Zaldívar and Guillier, 1977).

Anemia and leukopenia have been reported in infants ingesting approximately 3.5 mg As/day in contaminated milk over a period of 33 days (Hammamoto, 1955; as cited in ATSDR, 1989).

Premature birth and subsequent neonatal death was reported in a single individual following ingestion of arsenic (Lugo *et al.*, 1969).

Vascular diseases have long been noted to be associated with chronic arsenic exposures among German vineyard workers (Grobe, 1976) and inhabitants of Antofagasta, Chile (Borgono *et al*., 1977). Peripheral vascular diseases have been reported to be associated with the occurrence of arsenic in well waters in Taiwan (Chen and Wu, 1962; Chi and Blackwell, 1968; Tseng, 1977; Chen *et al*., 1988a).

Wu *et al*. (1989) found significant trends of mortality rates from peripheral vascular diseases and cardiovascular diseases with concentrations of arsenic in well water. However, no significant association was observed for cerebrovascular accidents. Engel and Smith (1994) evaluated arsenic in drinking water and mortality from vascular disease in 30 U.S. counties from 1968 to 1984. Mean As levels in drinking water ranged from 5.4 to 91.5 µg/L. Standardized mortality ratios (SMRs) for diseases of arteries, arterioles, and capillaries (DAAC) for counties exceeding 20 µg/L were 1.9 (90% C.I. = 1.7-2.1) for females and 1.6 (90% C.I. = 1.5-1.8) for males. SMRs for three subgroups of DAAC including arteriosclerosis and aortic aneurysm were also elevated as were congenital abnormalities of the heart and circulatory system.

Tseng *et al*. (1996) studied the dose relationship between peripheral vascular disease (PVD) and ingested inorganic arsenic in blackfoot disease endemic villages in Taiwan. A total of 582 adults (263 men and 319 women) underwent Doppler ultrasound measurement of systolic pressures on

bilateral ankle and brachial arteries and estimation of long-term arsenic exposure. The diagnosis of PVD was based on an ankle-brachial index of < 0.9 on either side. Multiple logistic regression analysis was used to assess the association between PVD and As exposure. A dose-response was observed between the prevalence of PVD and long-term As exposure. The odds ratios (95% confidence intervals) after adjustment for age, sex, body mass index, cigarette smoking, serum cholesterol and triglyceride levels, diabetes mellitus and hypertension were 2.77 (0.84-9.14), and 4.28 (1.26-14.54) for those who had cumulative As exposures of 0.1 to 19.9 and ≥ 20 (mg/L) x yr, respectively. A follow up study (Tseng *et al*., 1997) indicated that PVD was correlated with ingested As and not with abnormal lipid profiles. The lipid profiles studied were total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c), apolipoprotein AI, and apolipoprotein B. Other lipids such as modified LDL, subclasses of LDL and HDL, and other lipoproteins such as lipoprotein (a), which may track as better indicators of atherosclerosis, were not included. Also the roles of platelet aggregation and coagulation profiles were not studied.

Chen *et al*. (1996a) evaluated the dose-response relationship between ischemic heart disease (ISHD) mortality and long-term arsenic exposure. Mortality rates from ISHD among residents in 60 villages in an area of Taiwan with endemic arseniasis from 1973 through 1986 were analyzed for association with As concentrations in drinking water. Based on 1,355,915 person-years and 217 ISHD deaths, the cumulative ISHD mortalities from birth to age 79 yr were 3.4%, 3.5%, 4.7%, and 6.6% for the median As concentrations of < 0.1, 0.1-0.34, 0.35-0.59, and ≥ 0.6 mg/L, respectively. Multivariate-adjusted relative risks (RRs (95% C.I)) associated with cumulative arsenic exposure from well water were 2.46 (0.53-11.36), 3.97 (1.01-15.59), and 6.47 (1.88-22.24) for 0.1-9.9, 10.0-19.9, and 20+ (mg/L)yr, respectively, compared with those without As exposure.

Chiou *et al*. (1997b) evaluated the dose-response relationship between prevalence of cerebrovascular disease and ingested arsenic among residents of the Lanyang Basin in northeast Taiwan. A total of 8102 adults from 3901 households were recruited for the study. Arsenic in the well water of each household was determined by hydride generation and atomic absorption spectrometry. Logistic regression analysis was used to estimate multivariate-adjusted odds ratios and 95% confidence intervals for various risk factors of cerebrovascular disease. A significant dose-response relationship was observed between As concentration in well water and prevalence of cerebrovascular disease after adjustment for age, sex, hypertension, diabetes mellitus, cigarette smoking, and alcohol consumption. The dose-response was even more prominent for cerebral infarction with multivariate-adjusted odds ratios (95% C.I.) of 1.0, 3.4 (1.6-7.3), 4.5 (2.0-9.9), and 6.9 (3.0-16), respectively, for those who consumed well water with As concentration of 0, 0.1-50.0, 50.1-299.9, and >300 μg/L. For cumulative arsenic exposures of <0.1, 0.1-4.9, and ≥5.0 (mg/L)yr, the odds ratios were 1.00, 2.26, and 2.69 for cerebrovascular disease and 1.00, 2.66, and 3.39 for cerebral infarction, respectively. All of the values above for As exposed groups were significantly greater than unexposed at $p < 0.05$ or less.

Chen *et al*. (1995) also investigated the association between long-term exposure to inorganic arsenic and the prevalence of hypertension. A total of 382 men and 516 women were studied in villages where arseniasis was endemic. Hypertension was defined as a systolic blood pressure of 160 mm Hg or greater, or a history of hypertension treated with antihypertensive drugs. The

long-term arsenic exposure was calculated from the history of artesian well water consumption obtained through subject questionnaires and the measured arsenic concentration in well water. Residents in villages where long-term arseniasis was endemic had a 1.5-fold increase in age- and sex-adjusted prevalence of hypertension compared with residents in nonendemic areas. Duration of well water consumption, average As water concentration, and cumulative As exposure were all significantly associated with hypertension. For the cumulative As exposure in (mg/L)yr the percent prevalence values were: 0, 5.0%; 0.1-6.3 (mg/L)yr, 4.9%; 6.4-10.8 (mg/L)yr, 12.8%; 10.9-14.7 (mg/L)yr, 22.1%; 14.8-18.5 (mg/L)yr, 26.5%; > 18.5 (mg/L)yr, 29.2%. As part of a study of arsenic exposure via drinking water and mortality outcome in Millard County, Utah, Lewis *et al*. (1999) found a statistically significant association with mortality from hypertensive heart disease. Median drinking water concentration of arsenic ranged from 14 to 166 µg/L for the 946 subjects in the study. The standard mortality ratios (SMR) without regard to specific exposure levels were SMR = 2.20 (95% C.I., 1.36-3.36) for males and SMR = 1.73 (95% C.I., 1.11-2.58) for females. When analyzed by cumulative exposure groups of low (< 1.0 (mg/L)yr), medium (1.0-4.9 (mg/L)yr), and high (≥ 5.0 (mg/L)yr) there was no apparent dose response. However the cumulative dose estimates in this study were lower than in the Chen *et al*. (1995) discussed above so the results of the two studies are not inconsistent.

In a study related to those above, Lai *et al*. (1994) studied inorganic arsenic ingestion and the prevalence of diabetes mellitus. A total of 891 adult residents of villages in southern Taiwan where arseniasis is endemic were included in the study. Diabetes status was determined by an oral glucose tolerance test and a history of diabetes regularly treated with sulfonylurea or insulin. Cumulative arsenic exposure in ppm-yr was determined from the detailed history of drinking artesian well water. There was a dose-response relation between cumulative arsenic exposure and prevalence of diabetes mellitus. The relation remained significant after adjustment for age, sex, body mass index, and activity level at work by a multiple logistic regression analysis giving a multivariate-adjusted odds ratios of 6.61 and 10.05, respectively, for exposures of 0.1-15 ppm-yr and > 15.0 ppm-yr versus an unexposed group. In an effort to confirm this association between diabetes mellitus and arsenic observed for drinking water in Taiwan, Rahman and Axelson (1995) reviewed 1978 case-control data from a Swedish copper smelter. Twelve cases of diabetes mellitus (death certificate) were compared with 31 controls without cancer, cardiovascular and cerebrovascular disease. The odds ratios for diabetes mellitus with increasing arsenic exposure categories were 1.0 (reference level), 2.0, 4.2, and 7.0 with the 95% confidence level including unity. The trend was weakly significant, $p = 0.03$. Albeit with limited numbers the study provides some support for a role of arsenic exposure in the development of diabetes mellitus.

V. Effects of Animal Exposure

Changes in host resistance from inhalation exposure to As_2O_3 aerosol were examined in female CD1 mice using a streptococcus infectivity model and an assay for pulmonary bactericidal activity (Aranyi *et al.*, 1985; Aranyi *et al.*, 1981). Mice (100-200/group) were exposed to As_2O_3 aerosol (or filtered air) for 3 hours/day, 5 days/week, for 1, 5 or 20 days. Aerosol exposed and control mice were then combined before challenge with *Streptococcus zoopidemicus* aerosol (4-8 replicate exposures). Statistically significant increases in mortality ($p < 0.05$) were observed in

mice exposed (1) once to 271, 496, or 940 μg As/m^3, (2) 5 times to 519 μg As/m^3, and (3) 20 times to 505 μg As/m^3. Multiple exposures at a given exposure level did not correlate with increased mortality, suggesting an adaptation mechanism. Single exposure did, however, show a dose-response for increased mortality with increasing level of arsenic exposure. Bactericidal activity was evaluated by measuring the ratio of viable bacteria count to radioactive count in the lung 3 hours after infection with ^{35}S-labeled *Klebsiella pneumoniae*. A single exposure to 271, 496, or 940 μg As/m^3, but not to 123 μg As/m^3, resulted in significantly decreased bactericidal activity. Five exposures to 519 μg As/m^3 and twenty exposures to both 245 and 505 μg As/m^3 resulted in decreased bactericidal activity.

Female albino rats (20/group) were exposed to 0, 1.3, 4.9, or 60.7 μg As_2O_3/m^3 as aerosol continuously for 3 months (Rozenshtein, 1970). Decreased whole blood sulfhydryl group content, histological changes in the brain, bronchi, and liver, changes in conditioned reflexes, and changes in chronaxy ratio were observed in both the high- and mid-dose groups. (Chronaxy is the minimum time for which a current must flow, at a voltage twice the minimal current necessary to produce muscle stimulation, in order to cause a muscle to contract.) Among animals in the high dose group, eosinophilia, decreased blood cholinesterase activity, decreased serum sulfhydryl content, and increased blood pyruvic acid were observed. No significant changes were observed in the low-dose group.

Male mice (8-10/group) were exposed to 0, 0.5, 2.0, or 10.0 ppm sodium arsenite in drinking water for 3 weeks followed by a 28 day recovery period (Blakley *et al.*, 1980). The primary immune response of the spleen (as indicated by changes in IgM-production assayed by plaque-formation) was suppressed at all dose levels. The secondary immune response was also suppressed at all dose levels as indicated by a decrease in the number of IgG producing cells.

Male Sprague-Dawley rats (7-28/group) were exposed to 0, 40, 85, or 125 ppm sodium arsenate in drinking water for 6 weeks (Brown *et al.*, 1976). Rats from all arsenic exposed groups showed increased relative kidney weights, decreased renal mitochondrial respiration, and ultrastructural changes to the kidney.

Male ddY mice (number not stated) received 0, 3, or 10 mg As_2O_3/kg/day orally for 14 days and were examined for changes in concentrations of monoamine-related substances in various brain regions and for changes in locomotor activity (Itoh *et al.*, 1990). Locomotor activity was increased in the low-dose group and decreased in the high-dose group. Several monoamine-related compounds were altered in both dose groups in the cerebral cortex, hippocampus, hypothalamus, and corpus striatum.

Male and female Wistar rats (7-10/group) were treated from age 2 to 60 days by oral gavage with daily administration of 0 or 5 mg As/kg body weight (as sodium arsenate) (Nagaraja and Desiraju, 1993; Nagaraja and Desiraju, 1994). After 160 days, body weights, brain weights, and food consumption were decreased in the arsenic exposed group. Acetylcholinesterase (AChE) and glutamic acid decarboxylase (GAD) activity and gamma-aminobutyric acid (GABA) levels were decreased in the hypothalamus, brain stem, and cerebellum during the exposure period; all but AChE activity returned to normal during the post-exposure period. Changes in operant conditioning were also observed among the exposed animals.

Female Holtzman rats (>5/group) were treated with 0, 100, 500, 1000, 2000, or 5000 ppm As_2O_3 in feed for 15 days (Wagstaff, 1978). Hexobarbitone-induced sleeping time was altered in all arsenic exposed groups. Body weight and feed consumption were decreased among animals in the groups exposed to ≥ 500 ppm As_2O_3. Clinical signs of toxicity, observed among arsenic exposed animals, included roughened hair, diarrhea, and decreased physical activity.

Male Sprague-Dawley rats and C57 black mice (12/group) were treated with 0, 20, 40, or 85 ppm sodium arsenate in drinking water for up to 6 weeks (Woods and Fowler, 1978). Among arsenic exposed rats, heme synthetase activity was decreased in all exposed groups. Among animals exposed to ≥ 40 ppm sodium arsenate, hepatic ALA synthetase activity was decreased and urinary uroporphyrin and coproporphyrin were increased. Among exposed mice, heme synthetase activity was decreased and uroporphyrinogen I synthetase activity was increased in all exposed groups. Among animals exposed to ≥ 40 ppm sodium arsenate, urinary uroporphyrin and coproporphyrin were increased.

Administration of 3.7 mg As_2O_3/kg/day to rhesus monkeys for 12 months did not result in any neurologic change detectable by an EEG (Heywood and Sortwell, 1979). Two of the 7 animals exposed to this concentration died before the conclusion of the 52 week period. Of the surviving animals, two were retained for a 52 week recovery period after which they were necropsied. No significant changes in organ weights or gross appearance were noted.

Pregnant CFLP mice (8-11 females/group) were exposed to As_2O_3 for 4 hours/day on gestational days 9-12 at concentrations of 0, 0.26, 2.9, or 28.5 mg As_2O_3/m^3 (~0.2, 2.2, and 21.6 mg As/m^3 (Nagymajtényi *et al.*, 1985). A statistically significant decrease in fetal weight was observed in all the dose groups ($p < 0.05$), with a 3, 9, and 29% reduction in average fetal weight with increasing dose. Significantly increased fetal malformations were observed only in the highest dose group, primarily delayed ossification, with an apparent positive dose-related trend in the number of fetuses with malformations (3, 7, and 31, respectively). A similar dose-related trend in chromosome aberrations in liver cells was also observed in the number of cells with damage, chromatid gaps, chromatid breaks, chromosome fragments, and chromosome breaks. Only the number of damaged cells and chromosome breaks at the high dose were significantly different from the control ($p < 0.05$).

Data from Table 1 of Nagymajtényi *et al.* (1985).

As_2O_3 (mg/m^3)	*Number of litters*	*Living fetuses per mother*	*Number of fetuses examined*	*% dead fetuses*	*Average fetal weight (grams)*
28.5±0.3	11	9.6	100	29	0.981±0.04*
2.9±0.04	8	12.8.	100	13	1.146±0.03*
0.26±0.01	8	12.5	100	12	1.225±0.03*
0	8	12.5	100	8	1.272±0.02

* Significantly different from control ($p<0.05$)

Rats exposed to 1 μg As_2O_3/m^3 (0.76 μg As/m^3) for 5 months showed increased preimplantation mortality and delayed ossification in fetuses (Kamkin, 1982). Experimental detail was not presented, thus limiting the usefulness of this study.

A significant decrease in spermatozoa motility was observed in male rats following continuous exposure to 32.4 mg As_2O_3/m^3 for 48 hours (Kamil'dzhanov, 1982). Similarly, motility was decreased after (1) a 120 hour exposure to 7.95 mg/m^3, (2) a 252 hour exposure to 1.45 mg/m^3, and (3) an 800 hour exposure to 0.36 mg/m^3.

Holson *et al.* (1999) administered arsenic trioxide (As_2O_3) by whole body inhalation to groups of 25 Crl:CD (SD)BR female rats for six hours per day every day, beginning fourteen days prior to mating and continuing throughout mating. The target exposure levels were 0.3, 3.0, and 10.0 mg As_2O_3/m^3 (measured means: 0.24, 2.6, and 8.3 mg As/m^3). Maternal toxicity, evidenced by the occurrence of rales, a decrease in net body weight gain, and decreased food intake during pre-mating and gestation exposure, was observed only at the high dose. The NOAEL for maternal toxicity was 2.6 mg As/m^3 (3.4 mg As_2O_3/m^3). No treatment-related malformations or developmental variations were observed at any exposure level. The NOAEL for developmental toxicity was 8.3 mg As/m^3 (11 mg As_2O_3/m^3). The median mass aerodynamic diameter of particle sizes generated in the exposure chambers ranged from 1.9 to 2.2 μm for the three doses indicating that the dusts were respirable. However there were no blood or urine arsenic analytical data to assess delivered doses.

Nemec *et al*. (1998) evaluated the developmental toxicity of inorganic arsenic in mice and rabbits. CD-1 mice (25/dose group) and New Zealand White rabbits (20/dose group) were gavaged with aqueous arsenic acid (H_3AsO_4) doses of 0, 7.5, 24, or 48 mg/kg-d on gestation days (GD) six through 15 (mice) or 0, 0.19, 0.75, or 3.0 mg/kg-d on GD six through 18 (rabbits). The animals were examined at necropsy (GD 18, mice; GD 29, rabbits). Treatment related maternal toxicity including mortality (2/25) was observed only in the highest dose administered to mice. Effects on maternal weight gain were noted only on GD 6-9 ($p < 0.01$) and GD 15-18 ($p < 0.05$) of the mid dose and on GD 6-9 ($p < 0.05$) of the low dose. While overall maternal weight gains were statistically significantly reduced only at the top dose, there was an apparent negative trend in decreased GD18 body weights with increasing dose (56.2 g control, 54.9 g, 52.7g, and 46.7g, respectively). While the authors identified a NOAEL for maternal toxicity of 7.5 mg/kg-d, the apparent negative trend noted above suggests that this may be a LOAEL of 7.5 mg/kg-d (4.0 mg As/kg-d).

Statistically significant adverse effects on offspring growth or survival were seen only at the highest dose of 48 mg/kg-d. However, there was an apparent negative trend in the number of live fetuses per litter with increasing dose (12.3 control, 11.6, 11.0, and 6.6, respectively). An increased incidence of resorptions per litter was seen in the 48 mg/kg-d dose group ($p \leq 0.01$), (mainly early resorptions). Early and total resorptions showed an apparent positive trend (6.4% total control, 6.1%, 9.6%, and 41.9%, respectively). Mean fetal weight showed an apparent negative trend (1.3 g control, 1.32 g, 1.23 g, and 0.99 g, respectively). There were no statistically significant dose-related increases in the overall incidences of fetal malformations, however, the mean litter percent malformed was about three-fold higher in the 48 mg/kg-d dose

group than in the lower doses and control. The NOAEL for developmental toxicity would appear to be 7.5 mg/kg-d (4.0 mg As/kg-d).

Maternal toxicity in rabbits, including mortality, slight body weight loss, and clinical signs (decreased urination and defecation, occasional prostration and ataxia), occurred only at the high arsenic acid dose of 3.0 mg/kg-d. The number of does with decreased urination and defecation appeared to be slightly higher in the mid- and low-dose groups, but these effects may not have been treatment related and no effects on body weight were seen. At necropsy on GD 29 maternal body weight appeared to be reduced in the high dose group. A significant loss in mean maternal gravid body weight occurred during the first six days of high-dose treatment (GD 6-12) ($p \leq 0.01$). This effect persisted and was significantly different from controls for the entire treatment interval (GD 6-18). There were no statistically significant increases in the incidences of any developmental parameters, including malformations. Fetal survival, mean fetal weight, and sex ratio on GD 29 were not affected by the treatment. The number of live fetuses per litter was reduced and resorptions per litter increased in the high-dose group. The latter findings were mainly due to one doe with a totally resorbed litter. The overall values were the range from laboratory historical controls. The authors identified a NOAEL of 0.75 mg/kg-d (0.4 mg As/kg-d) for both maternal toxicity and developmental toxicity.

Stump *et al*. (1999) administered either sodium arsenate (As V) i.p. or arsenic trioxide (As III) i.p. or by gavage on GD 9 to 25 Crl:CD (SD) BR rats. The doses of sodium arsenate were 0, 5, 10, 20, and 35 mg/kg (0, 1.2, 2.4, 4.8, and 8.4 mg As/kg). The doses of arsenic trioxide were: i.p. 0, 1, 5, 10, and 15 mg/kg (0, 0.8, 3.8, 7.6, and 11.4 mg As/kg); and by gavage (p.o.) 0, 5, 10, 20, and 30 mg/kg (0, 3.8, 7.6, 15.2, and 22.7 mg As/kg). Sodium arsenate i.p. caused decreased maternal food consumption (GD 9-20), decreased body weights and body weight gains at the highest dose of 35 mg/kg. Decreased food consumption was also seen in the 20 mg/kg dose group at GD 9-10 and GD 9-20. Arsenic trioxide i.p. resulted in excessive mortality in the highest dose-group (19/25) and significant reductions in maternal food consumption, body weight at GD 20 , body weight change, and net body weight in the next highest dose-group (10 mg/kg). Arsenic trioxide p.o. resulted in less mortality in the highest dose-group (7/25). Clinical signs were noted in the 20 and 30 mg/kg dose-groups including changes in fecal consistency and decreased defecation. Food consumption (GD 9-10) was decreased in a dose-dependent manner across As treatment groups. The study identified single dose maternal effects NOAELs of 2.4 mg As/kg for sodium arsenate i.p. and 3.8 mg As/kg for arsenic trioxide i.p. A LOAEL of 3.8 mg As/kg was identified for arsenic trioxide p.o.

Intraperitoneal administration of sodium arsenate or arsenic trioxide caused neural tube and ocular defects (exencephaly, microphthalmia/anophthalmia, and other craniofacial defects) in the offspring of treated rats. These effects were statistically significant only at doses causing maternal toxicity or mortality (35 and 10 mg/kg, respectively). Oral administration of arsenic trioxide caused no treatment-related malformations. The study identified single dose developmental NOAELs of 2.4 mg As/kg for sodium arsenate i.p., 3.8 mg As/kg for arsenic trioxide i.p., and 15.2 mg As/kg for arsenic trioxide p.o.

DeSesso *et al*. (1998) in a comprehensive review of the developmental toxicity of inorganic arsenic concluded that cranial neural tube defects (NTDs) were induced in rodents only when

exposure occurred early in gestation, at high maternally toxic doses, and by parenteral routes of administration. They argued that such NTD effective doses are unlikely to be achieved by the oral, inhalation, or dermal routes in rodents and that inorganic arsenic does not represent a realistic developmental risk in humans subjected to any environmentally relevant exposure scenarios.

Male and female Charles River CD mice (10/group) were treated with 0 or 5 ppm arsenite in drinking water continuously through three generations (Schroeder and Mitchener, 1971). Endpoints examined included the interval between litters, the age at first litter, the ratio of males to females, the number of runts, stillborn offspring, failures to breed, and congenital abnormalities. The study showed an alteration in the number of small litters in the arsenic exposed group.

Female CD-1 mice (8-15/group) were treated by oral gavage with 0, 20, 40, or 45 mg sodium arsenite/kg on a single day of gestation between days 8 and 15 (Baxley *et al.*, 1981). Maternal mortality, fetal malformations, and increased prenatal death were observed among animals treated with 40 and 45 mg sodium arsenite/kg.

Pregnant golden hamsters (>10/group) were treated by oral gavage with a single administration of 0, 20, or 25 mg/kg sodium arsenite on one of gestational days 8-12 (Hood and Harrison, 1982). Prenatal mortality was increased among animals receiving 25 mg/kg on gestational days 8 and 12 and fetal weights were decreased among animals receiving 25 mg/kg on gestational day 12. One dam died following administration of 20 mg/kg.

Intravenous injection of radioactive arsenate (V) or arsenite (III) in several rodent species, including mice and hamsters, resulted in accumulation of arsenic in the lumen of the epididymal duct, which suggested that long term exposure of sperm to arsenic may occur *in vivo* following acute exposure (Danielsson *et al.*, 1984).

VI. Derivation of Chronic Reference Exposure Levels

Derivation of Inhalation Chronic Reference Exposure Level

Study	Nagymajtényi *et al*., 1985
Study population	CFLP mice (8-11/group)
Exposure method	Discontinuous inhalation exposure
Critical effects	Reduction in fetal weight; increased incidences of intrauterine growth retardation and skeletal malformations
LOAEL	200 μg As/m^3 (based on 0.26 mg/m^3 As_2O_3)
NOAEL	Not observed
Exposure continuity	4 hr/day
Exposure duration	4 days (gestational days 9-12)
Average experimental exposure	33 μg As/m^3 for LOAEL group (200 x 4/24)
Human equivalent concentration	33 μg As/m^3 for LOAEL group. (Due to the lack of aerosol particle size data for the critical study, a human equivalent concentration could not be developed using recommended methods of inhalation dosimetry.)
LOAEL uncertainty factor	10 (since USEPA severity level > 5)
Subchronic uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1000
Inhalation reference exposure level	0.03 μg As/m^3

Reports of human inhalation exposure to arsenic compounds, primarily epidemiological studies of smelter workers, indicate that adverse health effects occur as a result of chronic exposure. Among the targets of arsenic toxicity are the respiratory system (Lundgren, 1954), the circulatory system (Lagerkvist *et al.*, 1986), the skin (Perry *et al.*, 1948), the nervous system (Blom *et al.*, 1985), and the reproductive system (Nordstrom *et al.*, 1979). Occupational exposure levels associated with these effects ranged from 50 to 7000 μg As/m^3. These epidemiological studies suffer, however, from confounding as a result of potential exposure to other compounds, which limits their usefulness in the development of the chronic REL.

Studies in experimental animals show that inhalation exposure to arsenic compounds can produce immunological suppression, developmental defects, and histological or biochemical effects on the nervous system and lung, thus providing supportive evidence of the types of toxicity observed in humans. Among the inhalation studies, the lowest adverse effect level (LOAEL) was quite consistent:

245 μg As/m^3 for decreased bactericidal activity in mice (Aranyi *et al.*, 1985);
200 μg As/m^3 for decreased fetal weight in mice (Nagymajtényi *et al.*, 1985); and
270 μg As/m^3 for decreased sperm motility in rats (Kamil'dzhanov, 1982).

A single study showed effects occurring at 4.9 μg As_2O_3/m^3 (Rozenshtein, 1970), however, lack of detail with respect to endpoints and experimental design limits this study's usefulness. A

significant dose-related reduction in fetal weight and increased incidences of intrauterine growth retardation, skeletal malformations, and hepatocellular chromosomal aberrations were observed in mice following maternal inhalation exposure to 200 μg As/m^3 (260 μg As_2O_3/m^3) for 4 hours on gestation days 9, 10, 11, and 12 ($p<0.05$) (Nagymajtényi *et al.*, 1985). The most sensitive effect, decreased fetal weight, was observed at 200 μg As/m^3, so 200 μg As/m^3 was taken as a LOAEL. Maternal toxicity data were not reported.

The weight decrement of 3% might not be biologically significant if the loss is generally distributed. If it were specific, it could be. In humans, the logarithm of infant mortality (death) increases linearly as birth weight decreases from 3500 to 1000 grams (Hogue *et al*., 1987; Rees and Hattis, 1994). This log-linear relationship exists on both sides of the weight (2500 g) conventionally used as a cutoff defining low birth weight. There is no evidence for a threshold. Thus any reduction in fetal weight is a cause for concern since it increases mortality. In the absence of certainty, OEHHA staff take the health protective approach that the reduced weight effect in the animal fetuses may be biologically significant.

Route-to-route conversion of the LOAEL in the key study indicates that this chronic REL should also be protective of adverse effects that have been observed in studies with oral exposures, either in food or drinking water. Since adverse health effects have been reported among workers exposed to levels near 50 μg As/m^3, use of the human data would produce a chronic REL near that derived using animal data. The chronic REL from animal data should, therefore, be protective of potential adverse health effects from human exposures.

VII. Data Strengths and Limitations for Development of the REL

The major strength of the REL for arsenic is the identification of an animal LOAEL that is supported by data from other studies. The major uncertainties are the lack of adequate human inhalation data, the lack of a NOAEL observation, the lack of comprehensive, long-term, multiple-dose, multiple-species studies, and the possibly marginal significance of the findings in the low dose group in the Nagymajtényi *et al.* (1985) study.

In addition to being inhaled, airborne arsenic can settle onto crops and soil and enter the body by ingestion. Thus an oral chronic reference exposure level for arsenic is also required. We propose adopting the U.S. EPA's oral Reference Dose as the oral chronic REL for arsenic.

Derivation of Chronic Oral Reference Exposure Level (U.S. EPA RfD)

Study	Tseng *et al.*, 1968; Tseng, 1977
Study population	>40,000 residentially exposed individuals
Exposure method	Drinking water (residential exposures)
Critical effects	Hyperpigmentation, keratosis, and possible vascular complications
LOAEL	0.17 mg/L (0.014 mg/kg-day)
NOAEL	0.009 mg/L (0.0008 mg/kg-day)
Exposure continuity	Not applicable
Exposure duration	Lifetime
Average exposure	0.0008 mg/kg-day for NOAEL group
Human equivalent concentration	0.0008 mg/kg-day for NOAEL group
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	3
Cumulative uncertainty factor	3
Oral reference exposure level	0.0003 mg/kg bw-day

*Conversion Factors: NOAEL was based on an arithmetic mean arsenic concentration of 0.009 mg/L (in a range from 0.001 to 0.017 mg/L). This NOAEL also included estimation of arsenic from food. Since experimental data were missing, arsenic concentrations in sweet potatoes and rice were estimated as 0.002 mg/day. Other assumptions included consumption of 4.5 L water/day and 55 kg bw (Abernathy *et al.*, 1989).

NOAEL = [(0.009 mg/L x 4.5 L/day) + 0.002 mg/day] / 55 kg = 0.0008 mg/kg-day.

The LOAEL dose was estimated using the same assumptions as the NOAEL starting with an arithmetic mean water concentration from Tseng (1977) of 0.17 mg/L.

LOAEL = [(0.17 mg/L x 4.5 L/day) + 0.002 mg/day] / 55 kg = 0.014 mg/kg-day.

The oral REL is the U.S. EPA's oral Reference Dose (RfD) (U.S. EPA, 1996). The data reported in Tseng (1977) show an increased incidence of blackfoot disease that increases with age and dose. Blackfoot disease is a significant adverse effect. The prevalences (males and females combined) at the low dose are 4.6 per 1000 for the 20-39 year group, 10.5 per 1000 for the 40-59 year group, and 20.3 per 1000 for the >60 year group. Moreover, the prevalence of blackfoot disease in each age group increases with increasing dose. However, one report indicates that it may not be strictly due to arsenic exposure (Lu, 1990).

The data in Tseng *et al.* (1968) also show increased incidences of hyperpigmentation and keratosis with age. The overall prevalences of hyperpigmentation and keratosis in the exposed groups are 184 and 71 per 1000, respectively. The text states that the incidence increases with dose, but data for the individual doses are not shown. These data show that the skin lesions are the more sensitive endpoint. The low dose in the Tseng (1977) study is considered a LOAEL.

The control group described in Tseng *et al.* (1968; Table 3) shows no evidence of skin lesions and presumably blackfoot disease, although this latter point is not explicitly stated. This exposure of this group is considered a NOAEL. The arithmetic mean of the arsenic concentration in the wells used by the individuals in the NOAEL group is 9 µg/L (range: 1-17 µg/L) (Abernathy *et al.*, 1989). The arithmetic mean of the arsenic concentration in the wells used by the individuals in the LOAEL group is 170 µg/L (Tseng, 1977; Figure 4). Using estimates provided by Abernathy *et al.* (1989), the NOAEL and LOAEL doses for both food and water are as follows:

LOAEL - [170 µg/L x 4.5 L/day + 2 µg/day (contribution of food)] x (1/55 kg) = 14 µg/kg/day;
NOAEL - [9 µg/L x 4.5 L/day + 2 µg/day (contribution of food)] x (1/55 kg) = 0.8 µg/kg/day.

Although the control group contained 2552 individuals, only 957 (approximately 38%) were older than 20, and only 431 (approximately 17%) were older than 40. The incidence of skin lesions increases sharply in individuals above 20; the incidence of blackfoot disease increases sharply in individuals above 40 (Tseng, 1968; Figures 5, 6 and 7).

This study is less powerful than it appears at first glance. However, it is certainly the most powerful study available on humans exposed to arsenic. This study shows an increase in skin lesions, 22% (64/296) at the high dose vs. 2.2% (7/318) at the low dose. The average arsenic concentration in the wells at the high dose is 410 mg/L and at the low dose is 5 mg/L (Cebrian *et al.*, 1983; Figure 2 and Table 1) or 7 mg/L (cited in the abstract). The average water consumption is 3.5 L/day for males and 2.5 L/day for females. There were about an equal number of males and females in the study. For the dose estimates given below an average water consumption of 3 L/day was assumed by USEPA. No data are given on the arsenic exposure from food or the body weight of the participants (therefore 55 kg was assumed). The paper states that exposure times are directly related to chronological age in 75% of the cases. Approximately 35% of the participants in the study were more than 20 years old (Figure 1). Exposure estimates (water only) are:

high dose - 410 mg/L x 3 L/day x (1/55 kg) = 22 mg/kg/day;
low dose - 5-7 mg/L x 3 L/day x (1/55 kg) = 0.3-0.4 mg/kg/day.

The high-dose group shows a clear increase in skin lesions and is therefore designated a LOAEL. There is some question whether the low dose is a NOAEL or a LOAEL since there is no way of knowing what the incidence of skin lesions would be in a group where the exposure to arsenic is zero. The 2.2% incidence of skin lesions in the low-dose group is higher than that reported in the Tseng *et al.* (1968) control group, but the dose is lower (0.4 vs. 0.8 mg/kg/day). The Southwick *et al.* (1983) study shows a marginally increased incidence of a variety of skin lesions (palmar and plantar keratosis, diffuse palmar or plantar hyperkeratosis, diffuse pigmentation, and arterial insufficiency) in the individuals exposed to arsenic. The incidences are 2.9% (3/105) in the control group and 6.3% (9/144) in the exposed group. There is a slight, but not statistically significant increase in the percent of exposed individuals that have abnormal nerve conduction (8/67 vs. 13/83, or 12% vs. 16%) (Southwick *et al.*, 1983; Table 8). The investigators excluded all individuals older than 47 from the nerve conduction portion of the study. These are the individuals most likely to have the longest exposure to arsenic. Although neither the increased

incidence of skin lesions nor the increase in abnormal nerve conduction is statistically significant, these effects may be biologically significant because the same abnormalities occur at higher doses in other studies. The number of subjects in this study was insufficient to establish statistical significance. Table 3 (Southwick *et al.*, 1983) shows the annual arsenic exposure from drinking water. No data are given on arsenic exposure from food or the body weight (assume 70 kg). Exposure times are not clearly defined, but are >5 years, and dose groups are ranges of exposure. Exposure estimates (water only) are:

dosed group - 152.4 mg/year x 1 year/365 days x (1/70) kg = 6 µg/kg/day;
control group - 24.2 mg/year x 1 year/365 days x (1/70) kg = 0.9 µg/kg/day.

Again because there are no data for a group not exposed to arsenic, there is some question if the control group is a NOAEL or a LOAEL. The incidence of skin lesions in this group is about the same as in the low-dose group from the Cebrian *et al.* (1983) study. The incidence of abnormal nerve conduction in the control group is higher than that from the low-dose group in the Hindmarsh *et al.* (1977) study described below. The control dose is comparable to the dose to the control group in the Tseng *et al.* (1968) and Hindmarsh *et al.* (1977) studies. The dosed group may or may not be a LOAEL, since it is does not report statistically significant effects when compared to the control. This study shows an increased incidence of abnormal clinical findings and abnormal electromyographic findings with increasing dose of arsenic (Hindmarsh *et al.*, 1977; Tables III and VI). However, the sample size is extremely small. Percentages of abnormal clinical signs possibly attributed to As were 10, 16, and 40% at the low, mid and high doses, respectively. Abnormal EMG were 0, 17 and 53% in the same three groups. The exact doses are not given in the Hindmarsh *et al.* (1977) paper; however, some well data are reported in Table V. The arithmetic mean of the arsenic concentration in the high-dose and mid-dose wells is 680 and 70 µg/L, respectively. Figure 1 (Hindmarsh *et al.*, 1977) shows that the average arsenic concentration of the low-dose wells is about 25 µg/L. No data are given on arsenic exposure from food. We assume daily water consumption of 2 liters and body weight of 70 kg. Exposure times are not clearly stated. Exposure estimates (water only) are:

low - 25 µg/L x 2 L/day x (1/70) kg = 0.7 µg/kg/day;
mid - 70 µg/L x 2 L/day x (1/70) kg = 2 µg/kg/day; and
high - 680 µg/L x 2 L/day x (1/70) kg = 19 µg/kg/day.

The low dose is a no-effect level for abnormal EMG findings. However, because there is no information on the background incidence of abnormal clinical findings in a population with zero exposure to arsenic, there is no way of knowing if the low dose is a no-effect level or another marginal effect level for abnormal clinical findings. The low dose is comparable to the dose received by the control group in the Tseng (1977) and Southwick *et al.* (1983) studies.

The responses at the mid-dose do not show a statistically significant increase but are part of a statistically significant trend and are biologically significant. This dose is an equivocal NOAEL/LOAEL. The high dose is a clear LOAEL for both responses. As discussed previously there is no way of knowing whether the low doses in the Cebrian *et al.* (1983), Southwick *et al.* (1983), and Hindmarsh *et al.* (1977) studies are NOAELs for skin lesions and/or abnormal nerve conduction. However, because the next higher dose in the Southwick and Hindmarsh studies

only shows marginal effects at doses 3-7 times higher, the U.S.EPA felt comfortable in assigning the low doses in these studies as NOAELs. The Tseng (1977) and Tseng *et al.* (1968) studies are therefore considered superior for the purposes of developing an RfD and show a NOAEL for a sensitive endpoint. Even discounting the people less than 20 years of age, the control group consisted of 957 people that had a lengthy exposure to arsenic with no evidence of skin lesions.

The following is a summary of the defined doses in mg/kg-day from the principal and supporting studies:

1) Tseng (1977):	NOAEL = 0.0008;	LOAEL = 0.014
2) Cebrian *et al.* (1983):	NOAEL = 0.0004;	LOAEL = 0.022
3) Southwick *et al.* (1983):	NOAEL = 0.0009;	LOAEL = none (equivocal effects at 0.006)
4) Hindmarsh *et al.* (1977):	NOAEL = 0.0007;	LOAEL = 0.019 (equivocal effects at 0.002)

There was not a clear consensus among U.S. EPA scientists on the oral RfD. Applying the U.S. EPA's RfD methodology, strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value, i.e., 0.1 to 0.8 µg/kg/day. However, the RfD methodology, by definition, yields a number with inherent uncertainty spanning perhaps an order of magnitude. The U.S. EPA Work Group will evaluate new data, which possibly impact on the recommended RfD for arsenic, as it becomes available.

The U.S. EPA used an Uncertainty Factor (UF) of 3 to account for both the lack of data to preclude reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals. No modifying factor was used.

U.S. EPA stated its confidence in the oral RfD as: Study - Medium; Data Base - Medium; and RfD - Medium. Confidence in the chosen study is considered medium. An extremely large number of people were included in the assessment (>40,000) but the doses were not well-characterized and other contaminants were present. The supporting human toxicity data base is extensive but somewhat flawed. Problems exist with all of the epidemiological studies. For example, the Tseng studies do not look at potential exposure from food or other source. A similar criticism can be made of the Cebrian *et al.* (1983) study. The U.S. studies are too small in number to resolve several issues. However, the database does support the choice of NOAEL. It garners medium confidence. Medium confidence in the RfD follows.

A dose-response analysis was conducted on the data sets from Mazumder *et al*. (1998) using the benchmark dose software provided by U.S. EPA (BMDS, version 1.2, 1999). Since the response for keratosis ranged only to 11 percent, a response criterion of one percent was used rather than the usual five percent. A linear dose-response model was fit to the data for male skin keratoses. An effective dose (ED_{01}) of 58.5 µg As/L and a benchmark dose (BD_{01}) of 49.7 µg As/L were obtained. The fit of the model to the data was statistically acceptable (Chi-squared goodness of fit test, P = 0.16). Assuming an average body weight of 60 kg and daily water consumption of three L/d for the subject population, the BD_{01} would be equivalent to 2.5 µg As/kg-d. This value might be considered a chronic oral NOAEL for skin effects. Since a normal population was employed in the study a ten-fold uncertainty factor for intraspecies variability can be applied to

this value to obtain a health-protective, oral exposure criterion of 0.25 μg/kg-d. A similar analysis of the male hyperpigmentation data gave a lower value (0.09 μg/kg-d) but was rejected for poor model fit. Although differently derived, the value above is very similar to U.S. EPA's oral RfD of 0.3 μg/kg-d which is based on skin effects observed in an earlier study (see discussion above).

VIII. References

ACGIH. 1992. American Conference of Governmental Industrial Hygienists, Inc. Documentation of the threshold limit values and biological exposure indices. Sixth edition. Cincinnati, OH: ACGIH.

Abernathy CO, Marcus W, Chen C, Gibb H, and White P. 1989. Office of Drinking Water, Office of Research and Development, U.S. EPA. Memorandum to O. Cook, Office of Drinking Water, U.S. EPA and P. Preuss, Office of Regulatory Support and Scientific Management, U.S. EPA. Report on Arsenic (As) Work Group Meetings. February 23.

Aranyi C, Bradof JN, Fenters JD, Graham JA, and Miller FJ. 1981. Effects of inhalation of arsenic trioxide aerosols in the pulmonary defenses of mice. In: International Conference. Heavy Metals in the Environment. Commission of the European Communities and the World Health Organization. pp. 450-453.

Aranyi C, Bradof JN, O'Shea WJ, Graham JA, and Miller FJ. 1985. Effects of arsenic trioxide inhalation exposure on pulmonary antibacterial defenses in mice. J. Toxicol. Environ. Health 15:163-172.

ATSDR. 1989. Agency for Toxic Substances and Disease Registry. US Public Health Service. Toxicological profile for arsenic. Prepared by Life Systems, Inc. under contract No. 68-02-4228.

Baxley MN, Hood RD, Vedel GC, Harrison WP, and Szczech GM. 1981. Prenatal toxicity of orally administered sodium arsenite in mice. Bull. Environ. Contam. Toxicol. 26:749-756.

Blakley BR, Sisodia CS, and Mukkur TK. 1980. The effect of methylmercury, tetraethyl lead and sodium arsenite on the humoral immune response in mice. Toxicol. Appl. Pharmacol. 52:245-254.

Blom S, Lagerkvist B, and Linderholm H. 1985. Arsenic exposure to smelter workers. Scand. J. Work Environ. Health 11:265-269.

Borgono JM, Vicent P, Venturino H and Infante A. 1977. Arsenic in the drinking water of the city of Antofagasta: epidemiological and clinical study before and after the installation of a treatment plant. Environ. Health Perspect. 19:103-105.

Brown MM, Rhyne BC, Goyer RA, and Fowler BA. 1976. Intracellular effects of chronic arsenic administration on renal proximal tubule cells. J. Toxicol. Environ. Health 1:505-514.

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System. (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

Cebrian ME, Albores A, Aguilar M, and Blakely E. 1983. Chronic arsenic poisoning in the north of Mexico. Human Toxicol. 2: 121-133.

CRC. 1994. CRC Handbook of Chemistry and Physics, 75th edition. Lide DR, ed. Boca Raton, FL: CRC Press Inc.

Chen CJ, Wu MM, Lee SS, Wang JD, Cheng SH, and Wu HY. 1988. Atherogenicity and carcinogenicity of high-arsenic artesian well water: multiple risk factors and related malignant neoplasms of blackfoot disease. Arteriosclerosis 8:452-460.

Chen CJ, Hsueh YM, Lai MS, Shyu MP, Chen SY, Wu MM, Kuo TL, and Tai TY. 1995. Increased prevalence of hypertension and long-term arsenic exposure. Hypertension 25:53-60.

Chen CJ, Chiou HY, Chiang MH, Lin LJ, and Tai TY 1996. Dose-response relationship between ischemic heart disease mortality and long-term arsenic exposure. Atheroscler. Thromb. Vasc. Biol. 16:504-510.

Chen KP and Wu HY. 1962. Epidemiologic studies on blackfoot disease: II. A study of source of drinking water in relation to the disease. J. Formosan Med. Assoc. 61:611-618

Chi IC and Blackwell RQ 1968. A controlled retrospective study of blackfoot disease, an endemic peripheral gangrene disease in Taiwan. Am. J. Epidemiol. 88:7-24.

Chiou HY, Huang YI, Su CL, Chang SF, Hsu YH, and Chen CJ. 1997. Dose-response relationship between prevalence of cerebrovascular disease and ingested inorganic arsenic. Stroke 28:1717-1723.

Danielsson BRG, Dencker L, Lindgren A, and Tjalve H. 1984. Accumulation of toxic metals in male reproductive organs. Arch. Toxicol. Suppl, 7:177-180.

Engel RR and Smith AH 1994. Arsenic in drinking water and mortality from vascular disease: an ecologic analysis in 30 U.S. counties. Arch. Environ. Health 49:418-427.

Grayson M. (ed.) 1978. Kirk-Othmer Encyclopedia of Chemical Technology. Third ed. New York, NY: John Wiley and Son, pp. 247-251.

Grobe JW 1976. Periphere Durchblutungsstorungen und Akrocyanose bei Arsengeschadigten Moselwintzern.[Peripheral circulatory disorders and acrocyanosis in Moselle valley vineyard workers with arsenic poisoning]. Berufsdermatosen 24:78-84.

Hammamoto E. 1955. Infant arsenic poisoning by powdered milk. Japanese Medical Journal 1649:2-12 [cited in ATSDR, 1989].

Heywood R, and Sortwell RJ. 1979. Arsenic intoxication in the rhesus monkey. Toxicol. Lett. 3:137-144.

Hindmarsh JT, McLetchie OR, Hefferman LPM *et al.* 1977. Electromyographic abnormalities in chronic environmental arsenicalism. J. Anal. Toxicol. 1:270-276.

Hogue CJ, Buehler JW, Strauss LT, and Smith JC. 1987. Overview of the National Infant Mortality Surveillance (NIMS) project - design, methods, results. Public Health Rep. 102(2):126-138.

Holson JF, Stump DG, Ulrich CE, and Farr CH. 1999. Absence of prenatal developmental toxicity from inhaled arsenic trioxide in rats. Toxicol. Sci. 51:87-97.

Hood RD, and Harrison WP. 1982. Effects of prenatal arsenite exposure in the hamster. Bull. Environ. Contam. Toxicol. 29:671-678.

HSDB. 1995. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, Maryland (TOMES® CD-ROM Version). Denver, CO: Micromedex, Inc. (Edition expires 7/31/96).

Itoh T, Zhang YF, Murai S, Saito H, Nagahama H, Miyate H, Saito Y, and Abe E. 1990. The effect of arsenic trioxide on brain monoamine metabolism and locomotor activity of mice. Toxicol. Lett. 54:345-353.

Kamil'dzhanov AX. 1982. Hygienic basis for the maximum permissible concentration of the arsenic trioxide in the ambient air. Gig. Sanit. 2:74-75.

Kamkin AB. 1982. For a revision of the maximum permissible concentration of arsenic trioxide in the ambient air of inhabited areas. Gig. Sanit. 1:6-9.

Lagerkvist B, Linderholm H, and Nordberg GG. 1986. Vasospastic tendency and Raynaud's phenomenon in smelter workers exposed to arsenic. Environ. Res. 39:465-474.

Lai MS, Hsueh YM, Chen CJ, Shyu MP, Chen SY, Kuo TL, Wu MM, and Tai TY. 1994. Ingested inorganic arsenic and prevalence of diabetes mellitus. Am. J. Epidemiol. 139:484-492.

Lewis DR, Southwick JW, Ouellet-Hellstrom R, Rench J and Calderon RL 1999. Drinking water arsenic in Utah: A cohort mortality study. Environ. Health Perspect. 107,:359-365.

Lu FJ. 1990. Blackfoot disease: arsenic or humic acid? Lancet 336(8707):115-116.

Lugo G, Cassady G, and Palmisano P. 1969. Acute maternal arsenic intoxication with neonatal death. Am. J. Dis. Child. 117:328-330.

Lundgren KD. 1954. [Damage to respiratory organs in workers in a smelting plant]. Nor. Hyg. Tidskr. 3:66-82 [cited in U.S. EPA, 1984].

Mazumder DNG, Haque R, Ghosh N, De BK Santra A, Chakraborty D, and Smith AH. 1998. Arsenic levels in drinking water and the prevalence of skin lesions in West Bengal, India. Int. J. Epidemiol. 27:871-877.

Morris JS, Schmid M, Newman S, Scheuer PJ, and Sherlock S. 1974. Arsenic and noncirrhotic portal hypertension. Gastroenterology, 64:86-94.

Nemec MD, Holson, JF, Farr CH, and Hood RD. 1998. Developmental toxicity assessment of arsenic acid in mice and rabbits. Reprod. Toxicol. 12:647-658.

Nagaraja TN, and Desiraju T. 1993. Regional alterations in the levels of brain biogenic amines, glutamate, GABA, and GAD activity due to chronic consumption of inorganic arsenic in developing and adult rats. Bull. Environ. Contam. Toxicol. 50:100-107.

Nagaraja TN, and Desiraju T. 1994. Effects on operant learning and brain acetylcholine esterase activity in rats following chronic inorganic arsenic intake. Hum. Exp. Toxicol. 13:353-356.

Nagymajtényi L, Selypes A, and Berencsi G. 1985. Chromosomal aberrations and fetotoxic effects of atmospheric arsenic exposure in mice. J. Appl. Toxicol. 5:61-63.

Nordstrom S, Beckman L, and Nordenson I. 1979. Occupational and environmental risks in and around a smelter in northern Sweden. V. Spontaneous abortion among female employees and decreased birth weight in their offspring. Hereditas 90:291-296.

Perry K, Bowler RG, Buckell HM, Druett HA, and Scilling RSF. 1948. Studies in the incidence of cancer in a factory handling inorganic compounds of arsenic. II. Clinical and environmental investigations. Br. J. Ind. Med. 5:6-15.

Rahman M and Axelson O. 1995. Diabetes mellitus and arsenic exposure: a second look at case-control data from a Swedish copper smelter. Occup. Environ. Med. 52:773-774.

Rees DC, and Hattis D. 1994. Chapter 8. Developing Quantitative Strategies for Animal to Human Extrapolation. In: Principles and Methods of Toxicology. Third ed. AW Hayes (ed.). New York: Raven.

Rozenshtein IS. 1970. [Sanitary toxicological assessment of low concentrations of arsenic trioxide in the atmosphere]. Gig. Sanit. 35:16-21.

Schroeder HA, and Mitchener M. 1971. Toxic effects of trace elements on reproduction of mice and rats. Arch Environ. Health 23:102-106.

Southwick JW, Western AE, Beck MM, *et al.* 1983. An epidemiological study of arsenic in drinking water in Millard County, Utah. In: Arsenic: Industrial, Biomedical, Environmental

Perpsectives. Lederer WH, and Fensterheim RJ, eds. New York: Van Nostrand Reinhold Co., pp. 210-225.

Stump DG, Holson JF, Fleeman TL, Nemec MD, and Farr CH. 1999. Comparative effects of single intraperitoneal or oral doses of sodium arsenate or arsenic trioxide during in utero development. Teratology 60:283-291.

Tseng CH, Chong CK, Chen CJ, and Tai TY 1996. Dose-response relationship between peripheral vascular disease and ingested inorganic arsenic among residents in blackfoot disease endemic villages in Taiwan. Atherosclerosis 120:125-133.

Tseng CH, Chong CK, Chen CJ, and Tai TY. 1997. Lipid profile and peripheral vascular disease in arseniasis-hyperendemic villages in Taiwan. Angiology 48:321-335.

Tseng WP. 1977. Effects and dose-response relationships of skin cancer and blackfoot disease with arsenic. Environ. Health Perspect. 19:109-119.

Tseng WP, Chu HM, How SW, Fong JM, Lin CS, and Yeh S. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J. Natl. Cancer Inst. 40:453-463.

U.S. EPA 1984. United States Environmental Protection Agency. Health Assessment Document for Inorganic Arsenic. EPA-600/8-83-012F. Final Report. U.S. EPA Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment. Research Triangle Park, NC: U.S. EPA. pp. 5-20.

U.S. Environmental Protection Agency. 1996. Integrated Risk Information System (IRIS) Database.

Vallee BL, Ulmer DD, and Wacker WEC. 1960. Arsenic toxicology and biochemistry. Arch. Ind. Health, 21:132-151.

Wagstaff DJ. 1978. Alteration of hepatic detoxification enzyme activity by dietary arsenic trioxide. Food Cosmet. Toxicol. 16:423-426.

Woods JS, and Fowler BA. 1978. Altered regulation of mammalian hepatic heme biosynthesis and urinary porphyrin excretion during prolonged exposure to sodium arsenate. Toxicol. Appl. Pharmacol. 43:361-371.

Wu MM, Kuo TL, Hwang YH, and Chen CJ. 1989. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. Am. J. Epidemiol. 130:1123-1132.

Zaldívar R, and Guillier A. 1977. Environmental and clinical investigations on endemic chronic arsenic poisoning in infants and children. Zentralbl. Bakt. Hyg. 1 Abt. Orig. B 165:226-234.